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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/596,012	SANDBERG ET AL.	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-2, 4-5, 7-10, 12-14, 18, 21, 26-28, 30-34, 38 and 46-58* is/are pending in the application.

4a) Of the above claim(s) *33,34 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,7-10,12-14,18,21,26-28,30-32 and 46-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/18/07; 10/29/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-2, 4-5, 7-10, 12-14, 18, 21, 26-28, 30-34, 38 and 46-58 are pending.

Applicant's election with traverse of Group II, (now claims 1-2, 4-5, 7-10, 12-14, 18, 21, 26-28, 30-32 and 46-58), drawn to a conjugate comprising a) a trifunctional cross-linking moiety, to which is coupled b) an affinity ligand via a linker 1, c) a cytotoxic agent, optionally via a linker 2, and d) an anti Erb antibody or variants thereof having the ability to bind to Erb antigens expressed on mammalian tumor surfaces with an affinity-binding constant of at least 5x 10^6 M^{-1} wherein the affinity ligand is biotin, or a biotin derivative having essentially the same binding function to avidin or streptavidin as biotin, wherein stability towards enzymatic cleavage of the biotinamide bond has been introduced in linker 1, the anti-Erb antibody or variants thereof are direct to Erb2, a composition and kit comprising said conjugate, filed November 24, 2010, is acknowledged.

The traversal is on the grounds that claims as amended contained the following special technical feature "wherein in average 2-4 molecules of the part a) to c) above are linked to the anti-Erb antibody. None of the cited documents teaches or suggests the claimed conjugate and improved ways of cancer treatment.

Applicants' traversal has been fully considered but is not deemed persuasive. While the claims may have been amended, the special technical feature "wherein in average 2-4 molecules of the part a) to c) above are linked to the anti-Erb antibody is taught by WO 97/29114 publication (published August 14, 1997; PTO 1449) in view of WO 99/55367 publication (published November 4, 1999; PTO 1449).

The WO 97/29114 publication teaches a conjugate comprising a) a trifunctional cross-linking moiety such as 5-N-Boc amino isophthoyl ditetrafluorophenyl ester (see paragraph bridging pages 9 and 10 of the reference, in particular), to which is coupled to b) an affinity ligand such as biotin (see page 6, Figure 1, in particular) or biotin derivative such as iminobiotin shown in structure 4 that has binding

affinity to avidin or streptavidin (see page 6, in particular) wherein the biotin moiety has been modified by introducing a steric group alpha to the amine to provide resistance to cleavage by biotindase (cleavage of the biotinamide bond), see paragraph bridging pages 17 and 18, in particular). The reference conjugate further comprises a targeting moiety such as monoclonal antibody or binding fragment thereof such as $F(ab')_2$, Fab, scFv or $scFv_2$ that binds to or target therapeutic agent or diagnostic agent to tumor (see page 18, line 15, page 27, line 10-17, page 38, page 10-15, in particular). The reference therapeutic agent is radiohalogenated moiety such as ^{18}F, (see page 38, Summary of invention, page 27, line 7, pages 41-42, page 21, lines 3-13, in particular) or radionuclide moiety such as boron-10, ^{211}At (see claim 18 of the reference, page 21, line 15-18, in particular). The reference biotin or biotin derivative contains ethers, amine, thioesters or thiols in the linker 1 (see claim 3 of the reference, page 38, in particular). The reference conjugate comprises an average of dimer (see page 35), trimer or multimers of biotin linked to the targeting moiety (see pages 27, line 10-17, pages 38-39, claim 20 of the reference, in particular). The reference linker moiety is about 8 to 20 atoms in length (see claim 7 of the reference, page 9, lines 7-13, page 17, in particular).

The WO 97/29114 publication does not teach the antibody is anti-Erb antibody or variants thereof having the ability to bind to Erb2 antigens with an affinity-binding constant of at least 5×10^6 M^{-1} such as trastuzumab.

However, the WO 99/55367 publication teaches various antibodies such as F5 and C1 that bind to ErbB2 with an affinity of at least 5×10^6 M^{-1} (see entire document, see page 31, first paragraph of page 32, Table 2 at page 60, in particular). The reference further teaches anti-ErbB-2 scFv antibody such as ErbB2 B7A, G11D, or A11A that has binding affinity of 0.22 to 0.49 $\times 10^{-9}$ M which is at least 5×10^6 M^{-1} (see page 60, lines 4-7, Table 2, in particular). The reference antibody may be conjugated to a drug or chemotherapeutic agent such as vinblastine or vindesine for targeting the reference drug to tumor cells expressing c-erbB-2 (see page 19, lines 10-14, in particular). The reference anti-ErbB2 antibody is useful

as a pharmaceutical composition for delivering effector molecules such as cytotoxin, a label, radionuclide or a drug to a cell bearing a c-erbB2 receptor for treating cancer (see claims 23-24, 26-27, 53 and 54 of the reference, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the monoclonal antibody or scFv antibody in the conjugate of the WO 97/29114 publication for the antibody that binds to ErbB2 with high affinity such at least 5 x 10^6 M^{-1} as taught by the WO 99/55367 publication to arrive at the claimed invention. Because Applicant's inventions do not contribute a special technical feature when viewed over the prior art, the inventions lack unity of invention. Therefore, the restriction requirement is still deemed proper and is therefore made FINAL.

Applicant is reminded that in the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Claims 33, 34 and 38 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

Claims 1-2, 4-5, 7-10, 12-14, 18, 21, 26-28, 30-32 and 46-58, drawn to a conjugate comprising a) a trifunctional cross-linking moiety, to which is coupled b) an affinity ligand via a linker 1, c) a cytotoxic agent, optionally via a linker 2, and d) an anti Erb antibody or variants thereof having the ability to bind to Erb antigens expressed on mammalian tumor surfaces with an affinity-binding constant of at least 5x 10^6 M^{-1} wherein the affinity ligand is biotin, or a biotin derivative having essentially the same binding function to avidin or streptavidin as biotin, wherein stability towards enzymatic cleavage of the biotinamide bond has been introduced in linker 1, the anti-Erb antibody or variants thereof are direct to Erb2, a composition and kit comprising said conjugate, are being acted upon in this Office Action.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on October 29, 2010 and October 18, 2007 have been considered by the examiner and an initialed copy of the IDS is included with this Office Action.

Specification

The use of the trademark MITRATAG 1033, Herceptin, MitraDept has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The disclosure is further objected to because of the following informalities: (A) “radio nuclide” at page 11, line 8, page 16, line 4 should be one word “radionuclide”. (B) The phrase “claims 33-45” at page 17, line 29 is objected to because said claims 33-45 have been canceled. (C) The punctuation marks in the phrase "Fab'. F(ab')2." should have been ",". (D) The phrase “anti Erb” should have been “anti-Erb” at page 25, line 3 and page 30, line 25. (E) Typographical error “F(ab’’) should have been “F(ab’)". Correction is required.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

Claims 1-2, 4, 5, 46 and 57 are objected to because of the following informality: “anti Erb antibody” should have been "anti-Erb antibody”. Appropriate correction is required.

Claim 5 is objected to because of the following informality: the plural “chemotherapeutic agents”, “immunostimulating agents”, "non-radioactive elements”, “photoactive compounds” should have been singular “chemotherapeutic agent”, “immunostimulating agent”, "non-radioactive element”, “photoactive compound”, respectively.

Claim 10 is objected to because said claim depends from canceled claim 6.

Claim 30 is objected to because “comprising a conjugate according to claim 1" should have been "comprising the conjugate according to claim 1". Claim 30 is further objected to because claim 30 should be a kit comprising the composition of claim 28 or the conjugate of claim 1.

Claim 46 is objected to because “F(ab’)2” should have been “$F(ab')_2$”.

Claim 46 is further objected to because of the typographical error “F(ab’’)". Neither the specification nor the art defines what “F(ab’’)" is.

Claim 51 is objected to because said claim depends from canceled claim 16.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8, 13, 18, 21 26-28, 30, 31, 46, 48, 49, 50, 52, 54, 56 and 58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 8, 13, 18, 21, 26, 31, 48, 49, 50, 52, 54, 56 and 58, the phrase "preferably" renders the claims indefinite because the metes and bounds of what would constitute a "preferably" cannot be determined.

Regarding claim 27, the phrase "i.e." renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention.

Regarding claim 30, part of claim 30 encompasses a kit comprising the conjugate of claim 1 which comprises biotin and the last part of claim 30 also encompasses any medical composition and an extracorporeal device comprising immobilized receptor onto which the affinity ligand binds which lack biotin (claim 32). It is unclear what is encompasses in the kit of claim 30. Clarification is required.

Regarding claim 46, the phrase "essentially similar" renders the claim indefinite because the metes and bounds of what would constitute "essentially similar" cannot be determined. The term "essentially similar" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree of similarity, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Regarding claim 48, the phrase "wherein the radionuclide…wherein the chemotherapeutic agent" has no antecedent basis in base claim 10. Claim 10 recites cytotoxic agent. Claim 48 should depend from claim 47.

Regarding claim 54, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Regarding claim 26, 27 and 28, the term "it" renders the claims indefinite because it is unclear whether "it" is referring to the conjugate or the composition or the cross-linking moiety, or the affinity ligand or the cytotoxic agent or the anti-Erb antibody or any one of the linker such as linker 1 or linker 2.

Claim rejections under - 35 U.S.C. 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-5, 7-10, 12-14, 18, 21, 26, 28, 30-32 and 46-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to numerous conjugate comprising variants of anti-Erb antibodies, or variants of any Erb2 antibodies, any antibodies and antigens/haptens or any proteins and cofactors as affinity ligand or affinity ligand is absent and any and all other molecule having the same or similar effect directly or indirectly on cancer cells or cancer tissues as toxic agent, derivative of any radionuclides, any derivatives, or mutants or fragments of avidin or streptavidin wherein said term would encompass a vast collection of reagents that are not disclosed in the specification or known in the prior art and wherein the

structure of said reagents is unpredictable (for example nonprotein reagents, mutants of known antibodies, etc).

The specification discloses just one trastuzumab (HERCEPTIN®) that binds to human ErbB2. The specification discloses conjugate set forth in claim 27.

The antibodies which bind Erb encompass any Erb antigen derived from any animal species and it is unclear as to what Erb molecules other than those of human or mouse were known in the art. The identity of the Erb molecules such as Erb2 from the thousands of different types of mammals for which Erb has not been described is unpredictable. Thus, the written description provided in the specification is not commensurate with the scope of the claimed inventions.

With respect to antibody variants that encompass substitutions, deletion, addition and combination thereof, there is insufficient description as to where and what amino acids within which antibody that can be altered and still maintains binding specificity to human ErbB2.

There is no information regarding what structural features, i.e., six CDRs of immunoglobulin heavy and light chain of the encompassed antibodies would likely be associated with which binding specificity, i.e., binding specifically to Erb from human as opposed to other species because the specification does not describe the complete structure, partial structures or physical properties associated with such antibodies. The structure-function correlation set forth in the disclosure does not clearly allow persons of ordinary skill in the art to recognize that the applicant has in fact invented what is claimed because the disclosure only sets forth adequate written description for trastuzumab but not any Erb antibody, any Erb2 antibody or variant thereof with an affinity-binding constant of at least 5×10^6 M^{-1}. Thus, the functional definition (i.e., at least 5×10^6 M^{-1}) cannot be correlated with the disclosed structures.

Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al

(Proc. Natl. Acad. Sci. USA 1982 Vol. 79 page 1979 ; PTO 892). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. A method of treating cancer in the absence of in vivo working example is unpredictable.

For example, Stancoviski et al. (Proceedings of the National Academy of Science USA 88: 8691-8695, 1991, PTO 892) characterized the binding effects upon the growth of tumor cells of different antibodies, each of which bind different epitopes of the extracellular domain of a tumor-associated antigen related to EGFR, namely ErbB2; see entire document (e.g., the abstract). Stancovski et al. teaches some anti-ErbB2 antibodies inhibited tumor cell growth, but others actually accelerated their growth (page 8693, column 1).

Indeed, Riemer et al. (Mol. Immunol. 42: 1121-1124, 2005; PTO 892) teaches, because antibodies binding the same antigens have been shown to both ameliorate and aggravate disease symptoms, the concept of epitope specificity, as opposed to mere antigen specificity, in humoral immunology has gained importance in modern medicine the diverse biological effects; see entire document, particularly page 1123, column 1.

It follows from the above discussion of the related prior art that the mere generalized description of antibodies that bind a well-characterized antigen, as opposed to a well characterized epitope of an antigen, cannot always suffice to describe adequately antibodies that have, for example, an inhibitory or therapeutic effect, because the skilled artisan could not immediately envision, recognize, or distinguish those antibodies that bind an antigen on neoplastic cells and inhibit the growth of those neoplastic cells from antibodies that bind the antigen but lack therapeutic effect (e.g., promote the growth of neoplastic cells).

Thus, the prior art teaches the therapeutic effectiveness of an antibody that targets cancer cells is not a certainty, and is necessarily determined empirically; and consequently the disclosure cannot be

considered to reasonably convey to the skilled artisan Applicant's possession of the claimed invention, since it fails to describe with clarity and particularity the claimed antibody, which can be used as intended. Antibodies that bind to Erb are apparently no different.

For example, Cochran et al. (J. Immunol. Meth. 287: 147-158, 2004; PTO 892) describes two anti-EGFR antibodies that bind to spatially overlapping epitopes of EGFR; yet only one of the two competes with EGF for binding to the receptor; see entire document (e.g., page 156, column 1). Thus, an antibody that binds to the same region of EGFR, or perhaps even an antibody that binds to an isoform of EGFR that is expressed in certain cancer cells, but not normal cells, may not have therapeutic value in and of itself, unless it is conjugated to a cytotoxic moiety or capable of mediating antibody dependent cellular cytotoxicity or fixing complement. Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

While method of screening for antibody that binds to Erb2 with high affinity is known in the art, possession may not be shown by merely described how to obtain possession of members of the claimed genus or how to identify their common structural features. See University of Rochester, 358 F.3d at 927, 69 USPQ2d at 1895.

With regard to any “other molecule having the same or similar effect directly or indirectly on cancer cell or cancer tissue” (claim 5), there is a lack of disclosure as to the structure, i.e., amino acid sequence, chemical structure, or nucleotide sequence of such molecule associated with which particular effect directly or indirectly encompassed by the claim.

With regard to any “derivatives" in claims 8 and 12 and "antibodies and antigens or protein and cofactors" in claim 31, there is a lack of disclosure as to the structure, i.e., amino acid sequence, chemical structure, nucleotide sequence of such derivative. Likewise, there is a lack of disclosure as to the

structure, i.e., amino acid sequences of six CDRs associated with the unspecified antibodies that bind to which antigen or protein encompassed by the claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddles v.Baird, 30 USPQ2d 1481, 1483. In Fiddles v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences.

Therefore, only conjugates as set forth in claim 27 comprising trastuzumab as the antibody, trifunctional linking moiety selected from the group consisting of triaminobenzene, tricarboxybenzene, diacarboxyaniline, diamino benzoic acid and biotin or biotin derivative selected from the group consisting of the ones set forth in claim 13, a composition or kit comprising the conjugate of claim 27, but not the full breadth of the claims meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Claims 1-2, 4-5, 7-10, 12-14, 18, 21, 26, 28, 30-32 and 46-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a conjugate as set forth in claim 27, (2) a composition comprising the conjugate as set forth in claim 27 and a pharmaceutically acceptable excipient and (3) a kit comprising the conjugate as set forth in claim 27, **does not** reasonably provide enablement for any conjugates as set forth in claims 1-2, 4-5, 7-10, 12-14, 18, 21, 26, 28, 30-32 and 46-58. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn to numerous conjugate comprising any and all anti Erb antibodies such as any Erb2, or variants thereof, any antibodies and antigens/haptens or any proteins and cofactors as affinity ligand or affinity ligand is absent and any and all other molecule having the same or similar effect directly or indirectly on cancer cells or cancer tissues as toxic agent, derivative of any radionuclides, any derivatives, or mutants or fragments of avidin or streptavidin that encompass a vast collection of reagents that are not disclosed in the specification or known in the prior art and wherein the structure of said reagents is unpredictable (for example nonprotein reagents, mutants of known antibodies, etc).

The specification discloses just one trastuzumab (HERCEPTIN®) that binds to human ErbB2. The specification discloses conjugate set forth in claim 27.

The antibodies which bind Erb encompass any Erb antigen derived from any animal species and it is unclear as to what Erb molecules other than those of human or mouse were known in the art. The

identity of the Erb molecules such as Erb2 from the thousands of different types of mammals for which Erb has not been described is unpredictable. Thus, the written description provided in the specification is not commensurate with the scope of the claimed inventions.

With respect to antibody variants that encompass substitutions, deletion, addition and combination thereof, there is lack of specific guidance as to where and what amino acids within which antibody that can be altered and still maintains binding specificity to ErbB2.

There is no information regarding what structural features, i.e., six CDRs of immunoglobulin heavy and light chain of the encompassed antibodies would likely be associated with binding specificity, i.e., binding specifically to Erb from human as opposed to which Erb from other species.

Furthermore, even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA 1982 Vol. 79 page 1979). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Given the numerous conjugate comprising any and all Erb variants, there are insufficient in vivo working examples such conjugate could treat any cancer such as breast or ovarian cancer.

For example, Stancoviski et al. (Proceedings of the National Academy of Science USA 88: 8691-8695, 1991, PTO 892) characterized the binding effects upon the growth of tumor cells of different antibodies, each of which bind different epitopes of the extracellular domain of a tumor-associated antigen related to EGFR, namely ErbB2; see entire document (e.g., the abstract). Stancovski et al. teaches some anti-ErbB2 antibodies inhibited tumor cell growth, but others actually accelerated their growth (page 8693, column 1).

Indeed, Riemer et al. (Mol. Immunol. 42: 1121-1124, 2005; PTO 892) teaches, because antibodies binding the same antigens have been shown to both ameliorate and aggravate disease symptoms, the

concept of epitope specificity, as opposed to mere antigen specificity, in humoral immunology has gained importance in modern medicine the diverse biological effects; see entire document, particularly page 1123, column 1.

It follows from the above discussion of the related prior art that the mere generalized description of antibodies that bind a well-characterized antigen, as opposed to a well characterized epitope of an antigen, cannot always suffice to describe adequately antibodies that have, for example, an inhibitory or therapeutic effect, because the skilled artisan could not immediately envision, recognize, or distinguish those antibodies that bind an antigen on neoplastic cells and inhibit the growth of those neoplastic cells from antibodies that bind the antigen but lack therapeutic effect (e.g., promote the growth of neoplastic cells). Thus, the prior art teaches the therapeutic effectiveness of an antibody that targets cancer cells is not a certainty, and is necessarily determined empirically. Antibodies that bind to Erb are apparently no different.

For example, Cochran et al. (J. Immunol. Meth. 287: 147-158, 2004; PTO 892) describes two anti-EGFR antibodies that bind to spatially overlapping epitopes of EGFR; yet only one of the two competes with EGF for binding to the receptor; see entire document (e.g., page 156, column 1). Thus, an antibody that binds to the same region of EGFR, or perhaps even an antibody that binds to an isoform of EGFR that is expressed in certain cancer cells, but not normal cells, may not have therapeutic value in and of itself, unless it is conjugated to a cytotoxic moiety or capable of mediating antibody dependent cellular cytotoxicity or fixing complement.

With regard to any "other molecule having the same or similar effect directly or indirectly on cancer cell or cancer tissue" (claim 5), there is a lack of specification guidance and working examples as to the structure, i.e., amino acid sequence, chemical structure, nucleotide sequence of such molecule associated with the particular effect encompassed by the claim.

With regard to any “derivatives" in claims 8 and 12, "antibodies and antigens or protein and cofactors" in claim 31, there is a lack of specific guidance and in working examples as to where and what amino acids within which antibodies or protein or cofactors could be modified by substitution, deletions, additional or combination thereof as encompassed by the claim.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to any erb antibody, any erb antibody variants thereof, any erb2 antibody, any erb2 variants thereof encompassed any modifications, any mutants or any derivatives of avidin or streptavidin, any other molecules having the same or similar effect directly or indirectly on cancer cells or cancer tissues for the claimed conjugates. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 5, 12-13, 18, 21, 28, 46-50, 57 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/29114 publication (published August 14, 1997; PTO 1449) in view of WO 99/55367 publication (published November 4, 1999; PTO 1449) or WO 01/00244 (published Jan 2001; PTO 1449).

The WO 97/29114 publication teaches a conjugate comprising a) a trifunctional cross-linking moiety such as 5-N-Boc amino isophthoyl ditetrafluorophenyl ester (see paragraph bridging pages 9 and 10 of the reference, in particular), to which is coupled to b) an affinity ligand such as biotin (see page 6, Figure 1, in particular) or biotin derivative such as iminobiotin shown in structure 4 that has the weaker binding to avidin or streptavidin (see page 6, in particular) wherein the biotin moiety has been modified by introducing a steric group such as methyl group to provide resistance to cleavage by biotindase (cleavage of the biotinamide bond), see paragraph bridging pages 17 and 18, in particular). The reference conjugate further comprises a targeting moiety such as monoclonal antibody or binding fragment thereof such as $F(ab')_2$, Fab, scFv or $scFv_2$ that targets therapeutic agent or diagnostic agent to tumor cells (see page 18, line 15, page 27, line 10-17, page 38, page 10-15, in particular). The reference therapeutic agent is radiohalogenated moiety such as ^{18}F (see page 38, Summary of invention, page 27, line 7, pages 41-42, page 21, lines 3-13, in particular) or radionuclide moiety such as boron-10, ^{211}At (see claim 18 of the reference, page 21, line 15-18, in particular). The reference biotin or biotin derivative contains ethers, amine, thioesters or thiols in the linker 1 (see claim 3 of the reference, page 38, in particular). The reference conjugate comprises an average of dimer (see page 35), trimer or multimers of biotin linked to the targeting moiety (see pages 27, line 10-17, pages 38-39, claim 20 of the reference, in particular). The reference linker moiety such as linker 1, linker 2 or linker 3 is about 8 to 20 atoms in length (see claim 7 of the reference, page 9, lines 7-13, page 17, in particular).

The WO 97/29114 publication does not teach the anti-Erb antibody or variants thereof having the ability to bind to Erb2 antigens with an affinity-binding constant of at least $5 \times 10^6\ M^{-1}$ such as trastuzumab.

However, the WO 99/55367 publication teaches various antibodies such as F5 and C1 that bind to ErbB2 with an affinity of at least 5 x 10^6 M^{-1} (see entire document, see page 31, first paragraph of page 32, Table 2 at page 60, in particular). The reference further teaches anti-ErbB-2 scFv antibody such as B7A, G11D and A11A that have binding affinity of 0.22 to 0.49 x 10^{-9} M which is at least 5 x 10^6 M^{-1} (see page 60, lines 4-7, Table 2, in particular). The reference antibody may be conjugated to a drug or chemotherapeutic agent such as vinblastine or vindesine for targeting said drug to tumor cells expressing cerbB-2 (see page 19, lines 10-14, in particular). The reference anti-ErbB2 antibody is useful as a pharmaceutical composition for delivering effector molecules such as cytotoxin, a label, radionuclide or a drug to a cell bearing a c-erbB2 receptor for treating cancer (see claims 23-24, 26-27, 53 and 54 of the reference, in particular).

The WO 01/00244 publication teaches humanized antibody such as HERCEPTIN® that binds to ErbB2, which is also known in the art as trastuzumab (see entire document, page 43-44, in particular). The reference anti-ErbB2 antibody is conjugated to a toxic agent such as maytansinoid DM-1 (see abstract, example 2, in particular) and composition comprising such for treating cancer expressing ErbB2 (see page 39, claims 1-25 of the reference, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the monoclonal antibody or scFv antibody in the conjugate of the WO 97/29114 publication for the antibody that binds to ErbB2 with high affinity such at least 5 x 10^6 M^{-1} as taught by the WO 99/55367 publication or the trastuzumab antibody known in the art for treating cancer as taught by the WO01/00244.

One of ordinary skill in the art would have been motivated to and had an expectation of success at the time the invention was made to modify the conjugate of the WO 97/29114 publication in view of the WO 99/55367 publication because anti-ErbB2 antibody that binds with high affinity and capable of internalization which is useful as a pharmaceutical composition for delivering effector molecules such as

cytotoxin, a label, radionuclide or a drug into a cell bearing a c-erbB2 receptor for treating cancer as taught by the WO 99/55367 publication (see claims 23-24, 26-27, 53 and 54 of the reference, in particular).

One of ordinary skill in the art would have been motivated to and had an expectation of success at the time the invention was made to modify the conjugate of the WO 97/29114 publication in view of the WO 01/00244 publication because humanized anti-ErbB2 antibody such as trastuzumab is useful delivering cytotoxic agent such as maytansinoid to cancer cell expressing c-erbB2 receptor for treating cancer as taught by the WO 01/00244 publication (see abstract, claims 1-25 of the reference, in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to do so because the WO 97/29114 publication teaches biotin compound including modified biotin molecules conjugated with water soluble linker moieties to form biotin dimer, trimer or multimers and one more effectors improves water solubility and resistant to cleavage by serum enzyme biotinidase for use in in vivo applications (see page 5, in particular).

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007) and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

A) Combining prior art elements according known methods to yield predictable results.

B) Simple substitution of one known element for another to obtain predictable results.

C) Use of known technique to improve similar products in the same way.

D) Applying known technique to a known product ready for improvement to yield predictable results.

E) "Obvious to try" --- choosing form a finite number of identified, predictable solutions, with a reasonable expectation of success.

F) Some teachings, suggestion, or motivation in the prior art that would lead to one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

In this case, simple substitution of the antibody in the biotin trifunctional linking conjugate of the WO 97/29114 publication for the well known internalizable high affinity antibody that binds to ErbB-2 as taught by the WO 99/55367 publication or trastuzuamb humanized antibody that binds to ErbB2 as taught by WO 01/00244 publication would obtain predictable biotin anti-ErbB2 conjugate.

In this case, applying known technique of making antibody-biotin trifunctional linker conjugate of the WO 97/29114 publication to an anti-ErbB2 antibody that is known in the art would ready for improving the antibody-biotin conjugate in the same way. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Claims 1-2, 5, 7-10, 12-14, 18, 21, 26, 28, 30-31 and 46-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/02050 publication (published January 13, 2000; PTO 1449) in view of WO 99/55367 publication (published November 4, 1999; PTO 1449) or WO 01/00244 (published Jan 2001; PTO 1449).

The WO 00/02050 publication teaches a conjugate comprising a) a trifunctional cross-linking moiety such as triaminobenzene, tricarboxybenzene, dicarboxyanline and diaminobenzoic acid (see Figure at page 1, page 14, line 8-19, claims 1-2, in particular), to which is coupled to b) an affinity ligand such as biotin (see Figure 1, page 9, lines 10-25, in particular) or any biotin derivative thereof such as norbiotin, homobiotin, oxybiotin, iminobiotin, desthiobiotin, diaminobiotin, biotin sulfoxide, biotin sulfone that bind to avidin or streptavidin (see page 11, claims 3-7, in particular) via a linker 1 that contains hydrogen bonding atoms such as ethers, or thioesters, carboxylates, sulfonates, or ammonium

group to aid in water solubilization of the biotin in water (see page 15, lines 9-24, claim 9 of the reference, in particular), an effector agent such as radionuclide, Tc-99m, aryl halides, N2S2 N3S chelates for Tc, DTPA, derivatives Me-DTPA, CITC-DTPA, DOTA, TETA, ^{111}In, ^{90}Y, PB, Bi, Cu, Sm, Lu-^{177}, radionuclides (see page 11, lines 19 through page 13, claims 13-15, in particular) or toxin, or drug (see claim 11 of the reference, in particular). The reference linker 1 further comprises a methyl group or alpha carboxylate group in linker 1 (see claim 10 of the reference, in particular) or distance between the bicyclic rings of the biotin moiety as in norbiotin or homobiotin to provide stability toward enzymatic cleavage of the biotinamide bond (see page 15, lines 25-32, claim 7, in particular). The reference linker 1 may be may not be deminished by steric hindrance (see reference claim 8, in particular). The reference linker 2 may be excluded (see claim 16 of the reference, in particular) or a spacer length of 1-25 atoms and contains hydrogen bonding atoms, carboxylates, sulfonates, or ammonium groups (see claims 17-18 of the reference, in particular). The reference effector molecules include toxin, enzyme, immunosuppressive agent, immunostimulating agent, and radionuclide (see claim 29 of the reference, in particular). The publication also teaches a kit comprising the reference conjugate (see claims 28-30 of the reference, in particular). The publication also teaches extracorporeal device for removal of radiolabeled antibody such as avidin coated column (see page 5, line 33-36, in particular). Claim 26 is included in this rejection because it is an obvious variation of the reference teaching since trastuzumab can be linked to either the trifunctional cross-linking moiety or the second linker as taught by the WO 00/02050 publication.

The WO 00/02050 publication does not teach the anti-Erb antibody or variants thereof having the ability to bind to Erb2 antigens with an affinity-binding constant of at least 5 x 10^6 M^{-1} such as trastuzumab.

However, the WO 99/55367 publication teaches various antibodies such as F5 and C1 that bind to ErbB2 with an affinity of at least 5 x 10^6 M^{-1} (see entire document, see page 31, first paragraph of page 32, Table 2 at page 60, in particular). The reference further teaches anti-ErbB-2 scFv antibody such as B7A, G11D and A11A that have binding affinity of 0.22 to 0.49 x 10^{-9} M which is at least 5 x 10^6 M^{-1}

(see page 60, lines 4-7, Table 2, in particular). The reference antibody may be conjugated to a drug or chemotherapeutic agent such as vinblastine or vindesine for targeting said drug to tumor cells expressing cerbB-2 (see page 19, lines 10-14, in particular). The reference anti-ErbB2 antibody is useful as a pharmaceutical composition for delivering effector molecules such as cytotoxin, a label, radionuclide or a drug to a cell bearing a c-erbB2 receptor for treating cancer (see claims 23-24, 26-27, 53 and 54 of the reference, in particular).

The WO 01/00244 publication teaches humanized antibody such as HERCEPTIN® that binds to ErbB2, which is also known in the art as trastuzumab (see entire document, page 43-44, in particular). The reference anti-ErbB2 antibody is conjugated to a toxic agent such as maytansinoid DM-1 (see abstract, example 2, in particular) and composition comprising such for treating cancer expressing ErbB2 (see page 39, claims 1-25 of the reference, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the monoclonal antibody or scFv antibody in the conjugate of the WO 00/02050 publication for the antibody that binds to ErbB2 with high affinity such at least 5×10^6 M^{-1} as taught by the WO 99/55367 publication or the trastuzumab (HERCEPTIN®) antibody known in the art for treating cancer as taught by the WO01/00244 publication.

One of ordinary skill in the art would have been motivated to and had an expectation of success at the time the invention was made to modify the conjugate of the WO 00/02050 publication in view of the WO 99/55367 publication because anti-ErbB2 antibody that binds with high affinity and capable of internalization is useful as a pharmaceutical composition for delivering effector molecules such as cytotoxin, a label, radionuclide or a drug into a cell bearing a c-erbB2 receptor for treating cancer as taught by the WO 99/55367 publication (see claims 23-24, 26-27, 53 and 54 of the reference, in particular).

One of ordinary skill in the art would have been motivated to and had an expectation of success at the time the invention was made to modify the conjugate of the WO 00/02050 publication in view of the WO 01/00244 publication because humanized anti-ErbB2 antibody such as HERCEPTIN (also known as trastuzumab) is useful delivering cytotoxic agent such as maytansinoid to cancer cell expressing c-erbB2 receptor for treating cancer as taught by the WO 01/00244 publication (see abstract, claims 1-25 of the reference, in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to do so because the WO 00/02050 publication teaches biotin compound including modified biotin molecules conjugated with water soluble linker moieties to form biotin dimer, trimer or multimers and one more effectors improves water solubility and resistant to cleavage by serum enzyme biotinidase for use in in vivo applications (see page 5, in particular).

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007) and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

A) Combining prior art elements according known methods to yield predictable results.

B) Simple substitution of one known element for another to obtain predictable results.

C) Use of known technique to improve similar products in the same way.

D) Applying known technique to a known product ready for improvement to yield predictable results.

E) "Obvious to try" --- choosing form a finite number of identified, predictable solutions, with a reasonable expectation of success.

F) Some teachings, suggestion, or motivation in the prior art that would lead to one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

In this case, simple substitution of the antibody in the biotin trifunctional linking conjugate of the WO 00/02050 publication for the well known internalizable high affinity antibody that binds to ErbB-2 as taught by the WO 99/55367 publication or trastuzuamb humanized antibody that binds to ErbB2 as taught by WO 01/00244 publication would obtain predictable biotin conjugate.

In this case, applying known technique of making antibody-biotin trifunctional linker conjugate of the WO 00/02050 publication to a known antibody would ready for improving the antibody-biotin conjugate in the same way. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Claims 1-2, 4-5, 7-10, 12-14, 18, 21, 26-28, 30-31 and 46-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/02051 publication (published January 2000; PTO 892) in view of WO 99/55367 publication (PTO 1449) or WO 01/00244 publication (published January 2000; PTO 892).

WO 00/02051 publication discloses a conjugate comprising components a)-d) of claim 1 (see entire document, page 1, claims 1-24, page 6, in particular). The WO 00/02051 publication discloses use of affinity ligand such as biotin or biotin derivative such as norbiotin, homobiotin, oxybiotin, iminobiotin, desthiobiotin, diaminobiotin, biotin sulfoxide, biotin sulfone and cytotoxic agent such as DOTA in said conjugate (see claims 5, 14, page 12, in particular). The biomolecule use in the conjugate can be an antibody which binds tumors (see pages 6-7) wherein the conjugate also uses a radiolabeled effector (see page 6). The conjugate uses the same components recited in the claimed invention and would therefore bind the same number of antibody molecules. The WO 00/02051 publication teaches trifunctional cross-linking moiety such as triaminobenzene, tricarboxybenzene, diacarboxyaniline, and diaminobenzoic acid

(see page 16, claim 5, in particular). The reference trifunctional cross-linking moiety includes triaminobenzene, tricarboxybenzene, diacarboxyaniline or diaminobenzoic acid (see Figure at page 1, page 16, claims 2, in particular), to which is coupled to b) an affinity ligand such as biotin (see Figure 1, page 12, in particular) or any biotin derivative thereof such as norbiotin, homobiotin, oxybiotin, iminobiotin, desthiobiotin, diaminobiotin, biotin sulfoxide, biotin sulfone that bind to avidin or streptavidin (see page 12, lines 21-25, claims 5-6, in particular) via a linker 1 that contains hydrogen bonding atoms such as ethers, or thioether, carboxylates, sulfonates, or ammonium group to aid in water solubilization of the biotin in water (see pages 16-17, claims 8-10 of the reference, in particular). The reference effector agent is a radionuclide such as Tc-99m, aryl halides, N2S2 N3S chelates for Tc, DTPA, derivatives Me-DTPA, CITC-DTPA, DOTA, TETA, ^{111}In, ^{90}Y, PB, Bi, Cu, Sm, Lu-^{177} (see page 11, claims 11-15, in particular) or toxin, or drug (see page 11, claim 11 of the reference, in particular). The reference linker 1 further comprises a methyl group or alpha carboxylate group in linker 1 (see claim 9 of the reference, in particular) or distance between the bicyclic rings of the biotin moiety as in norbiotin or homobiotin to provide stability toward enzymatic cleavage of the biotinamide bond (see claim 7, in particular). The reference linker 1 may be may not be diminished by steric hindrance (see reference claim 8, in particular). The reference linker 2 may be excluded (see page 12, lines 1-5, claim 17 of the reference, in particular) or a spacer length of 1-25 atoms and contains hydrogen bonding atoms, carboxylates, sulfonates, or ammonium groups (see claims 18-19 of the reference, in particular). The reference linker 3 may be excluded (see page 12, lines 1-5, claim 21 of the reference, in particular) or a spacer length of 1-25 atoms and contains hydrogen bonding atoms, carboxylates, sulfonates, or ammonium groups (see claims 22-23 of the reference, in particular). The reference effector molecules include toxin, enzyme, immunosuppressive agent, immunostimulating agent or radionuclide (see claims 11 and 31 of the reference, in particular). The publication also teaches a kit comprising the reference conjugate (see claims 30-32 of the reference, in particular). The publication also teaches extracorporeal

device for removal of radiolabeled antibody such as avidin coated column (see claims 29-30, in particular). The reference conjugate is administered intravenously (see page 6, line 26, in particular). Claim 26 is included in this rejection because it is an obvious variation of the reference teaching since trastuzumab can be linked to either the trifunctional cross-linking moiety or the second linker as taught by the WO 00/02051.

The WO 00/02051 publication does not teach the anti-Erb antibody or variants thereof having the ability to bind to Erb2 antigens with an affinity-binding constant of at least 5 x 10^6 M^{-1} such as trastuzumab.

However, the WO 99/55367 publication teaches various antibodies such as F5 and C1 that bind to ErbB2 with an affinity of at least 5 x 10^6 M^{-1} (see entire document, see page 31, first paragraph of page 32, Table 2 at page 60, in particular). The reference further teaches anti-ErbB-2 scFv antibody such as B7A, G11D and A11A that have binding affinity of 0.22 to 0.49 x 10^{-9} M which is at least 5 x 10^6 M^{-1} (see page 60, lines 4-7, Table 2, in particular). The reference antibody may be conjugated to a drug or chemotherapeutic agent such as vinblastine or vindesine for targeting said drug to tumor cells expressing cerbB-2 (see page 19, lines 10-14, in particular). The reference anti-ErbB2 antibody is useful as a pharmaceutical composition for delivering effector molecules such as cytotoxin, a label, radionuclide or a drug to a cell bearing a c-erbB2 receptor for treating cancer (see claims 23-24, 26-27, 53 and 54 of the reference, in particular).

The WO 01/00244 publication teaches humanized antibody such as HERCEPTIN® that binds to ErbB2, which is also known in the art as trastuzumab (see entire document, page 43-44, in particular). The reference anti-ErbB2 antibody is conjugated to a toxic agent such as maytansinoid DM-1 (see abstract, example 2, in particular) and composition comprising such for treating cancer expressing ErbB2 (see page 39, claims 1-25 of the reference, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the monoclonal antibody or scFv antibody in the conjugate of the WO 00/02051

publication for the antibody that binds to ErbB2 with high affinity such at least 5 x 10^6 M^{-1} as taught by the WO 99/55367 publication or the trastuzumab (HERCEPTIN®) antibody linked to toxin known in the art for treating cancer as taught by the WO01/00244 publication.

One of ordinary skill in the art would have been motivated to and had an expectation of success at the time the invention was made to modify the conjugate of the WO 00/02051 publication in view of the WO 99/55367 publication because anti-ErbB2 antibody that binds to ErbB-2 with high affinity and capable of internalization is useful as a pharmaceutical composition for delivering effector molecules such as cytotoxin, a label, radionuclide or a drug into a cell bearing a c-erbB2 receptor for treating cancer as taught by the WO 99/55367 publication (see claims 23-24, 26-27, 53 and 54 of the reference, in particular).

One of ordinary skill in the art would have been motivated to and had an expectation of success at the time the invention was made to modify the conjugate of the WO 00/02051 publication in view of the WO 01/00244 publication because humanized anti-ErbB2 antibody such as HERCEPTIN (also known as trastuzumab) is useful delivering cytotoxic agent such as maytansinoid to cancer cell expressing c-erbB2 receptor for treating cancer as taught by the WO 01/00244 publication (see abstract, claims 1-25 of the reference, in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to do so because the WO 00/02051 publication teaches biotin compound including modified biotin molecules conjugated with water soluble linker moieties to form biotin dimer, trimer or multimers and one more effectors improves water solubility and resistant to cleavage by serum enzyme biotinidase for use in in vivo applications (see page 6, 17, in particular).

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007) and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and

incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

A) Combining prior art elements according known methods to yield predictable results.

B) Simple substitution of one known element for another to obtain predictable results.

C) Use of known technique to improve similar products in the same way.

D) Applying known technique to a known product ready for improvement to yield predictable results.

E) "Obvious to try" --- choosing form a finite number of identified, predictable solutions, with a reasonable expectation of success.

F) Some teachings, suggestion, or motivation in the prior art that would lead to one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

In this case, simple substitution of the antibody in the biotin trifunctional linking conjugate of the WO 00/02051 publication for the well known internalizable high affinity antibody that binds to ErbB-2 as taught by the WO 99/55367 publication or trastuzuamb humanized antibody that binds to ErbB2 as taught by WO 01/00244 publication would obtain predictable biotin conjugate.

In this case, applying known technique of making antibody-biotin trifunctional linker conjugate of the WO 00/02051 publication to an antibody would ready for improving the antibody-biotin conjugate in the same way. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9:

00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The IFW official Fax number is (571) 273-8300.

Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/

Primary Examiner, Art Unit 1644

December 30, 2010